

REMARKS

I. Introduction

Applicants gratefully acknowledge the PTO's withdrawal of all previously outstanding rejections based on 35 U.S.C. §§ 102 and 103. Now at issue in the present non-final Office Action are new grounds for rejection. Accordingly, Applicants respectfully request reconsideration of the present application in view of the foregoing amendments and in view of the reasons below.

II. Status of the Claims and Summary of Amendments Thereto

Claim 13 is canceled. Claims 1-12 and 14-21 are pending, and claim 2 is withdrawn from consideration. Claim 11 is amended to particularly point out that the agent is a precursor to protoporphyrin IX. Exemplary support for this amendment can be found in the specification at paragraphs 19 and 20. Claim 5 is amended to clarify the claimed method step, as illustrated, for example, in the specification at paragraphs 20 and 26. Claims 6-10 are amended to correct impermissible multiple dependencies.

III. The Office Action

Now having acknowledged, at least implicitly, Applicants' claims to priority, the PTO withdrew previous rejections under 35 U.S.C. §§ 102 and 103 in favor of a number of new grounds for rejection. Applicants now turn to those in the order presented.

A. Double Patenting

The PTO maintained its allegation that claims 1 and 3-21 are obvious over claims 1-12 of U.S. Patent No. 6,710,066, claims 1-12 of U.S. Patent No. 5,995,490, and claims 1 and 2 of U.S. Patent No. 5,211,938. Office Action at page 2. Applicants again request the PTO to hold these grounds for rejection in abeyance until such time as allowable subject matter has been indicated. At that time, should any double patenting concerns remain, Applicants will address the merits of the stated grounds for rejection.

B. Claim Objections

The PTO objected to claims 7-10 for impermissibly being multiple dependent claims depending from other multiple dependent claims. The amendments to the claims moot this objection.

C. Rejection of Claims Under 35 U.S.C. § 112, First Paragraph

**1. The Claims Enjoy Adequate Written Description
Because Protoporphyrin IV Precursors Were Well-
Known At the Time of Invention**

The PTO rejected claims 1, 3, 6, and 11-21 as allegedly lacking written description. Office Action at page 4. In particular, the PTO stated that the specification does not evidence descriptive support for the phrase “a precursor of protoporphyrin IX,” concluding that the skilled artisan would be unable to identify the compounds necessary for practice of the invention. *Id.* Insofar as the rejection might apply to the claims as amended, Applicants traverse the rejection.

The claims require that the administered agent is a precursor of protoporphyrin IX, which is sufficient to apprise the skilled artisan of what precursors were contemplated and possessed at the time of invention. The artisan would have understood that a precursor of protoporphyrin IX is a compound capable of participating, either directly or after an *in vivo* conversion, in the heme biosynthetic pathway and inducing synthesis of protoporphyrin IX. To illustrate the heme biosynthetic pathway, Applicants kindly refer the PTO to McGilvery et al., Biochemistry: A Fundamental Approach 632-635 (2d ed. 1979) (Exhibit 1). Showing the heme biosynthetic pathway, the excerpt illustrates the role of 5-aminolevulinate. Compounds useful in the invention include those compounds that are involved in the biosynthetic pathway of heme as shown in McGilvery et al.

Additionally, the present specification discloses at paragraph 0029 that “the usual rate-limiting step in the [heme biosynthetic] process, the synthesis of 5-aminolevulinic acid, can be bypassed by the provision of exogenous ALA, porphobilinogen or other precursor of PpIX.” The skilled artisan would understand an “other precursor” of protoporphyrin IX to include prodrugs of compounds in the heme biosynthetic pathway. Illustrative of an “other precursor” in this context is an ester of 5-aminolevulinic acid. Also, Applicants submit De Matties et al., “Brain 5-aminolaevulinate synthase,” Biochemical Journal, vol. 196, 811-817 (1981) (Exhibit 2). De Matties et al. disclose that “the methyl ester [of 5-aminolevulinic acid] reflects passive diffusion of the unchanged methyl ester across the blood/brain barrier, followed by hydrolysis to the free amino acid within the brain and subsequent conversion of 5-aminolaevulinate into haem.” The passage thus reflects knowledge at the time of the invention that an agent such as an ester of 5-aminolevulinic acid could be administered to a patient to achieve conversion into heme and, accordingly, achieve the synthesis of protoporphyrin IX (a precursor to heme).

Also, Applicants submit Srivastava et al., "Regulation of 5-Aminolevulinate Synthase mRNA in Different Rat Tissue, " Journal of Biological Chemistry, vol. 263, 5202-5209 (1988) (Exhibit 3) to further support the knowledge at the time of the invention that an ester of 5-aminolevulinic acid, such as the methyl ester, was known to enter the heme biosynthetic pathway via 5-aminolevulinic acid and therefore is active in inducing synthesis of protoporphyrin IX (a precursor to heme). Srivastava et al. disclose that "[a]dministration of hemin to rats reduced the basal level of this mRNA [a specific 5-aminolevulinate synthase] only in liver, but the heme precursor, 5-aminolevulinate (or its methyl ester) repressed the basal levels in liver, kidney, heart, testis and brain."

Therefore, at the time of the invention, the skilled artisan would have indeed appreciated what compounds are contemplated by the phrase "precursor of protoporphyrin IX." The precursors are substances such as 5-aminolevulinic acid as described in the present specification, the shown and listed precursors of PpIX as described by McGilvery in Biochemistry and esters of 5-aminolevulinic acid, such as the methyl ester of 5-aminolevulinic acid as described by Srivastava et al. and De Matties et al. Accordingly, the specification provides adequate written description of the claimed invention. Applicants therefore courteously request the PTO to reconsider and withdraw this ground for rejection.

**2. The Claims Are Enabled Because
Protoporphyrin IV Precursors Were
Well-Known At the Time of Invention**

The PTO rejected claims 1, 3, 6, and 11-21 for allegedly lacking enablement with respect to the full scope of "precursors of protoporphyrin IX." Office Action at page 4. According to the PTO, the specification allegedly lacks guidance or working examples, and so would have obliged the skilled artisan to engage undue experimentation to identify precursors other than 5-aminolevulinic acid for use in the claimed invention. *Id.* at page 5. Because the skilled person already would have apprehended what compounds qualify as precursors of protoporphyrin IX, the specification fully enables the claims, and Applicants therefore respectfully traverse this ground for rejection.

The PTO correctly mentioned but failed to consider all eight of the relevant factors in concluding that undue experimentation would be required to practice Applicants' invention. *See* MPEP § 2164.01(a) (Rev. 5, August 2006). "To make a valid rejection, one must evaluate all the facts and evidence and state why one would not expect to be able to extrapolate that one example across the entire scope of the claims." MPEP § 2164.02. Additionally, "[t]he specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known

to those skilled and already available to the public.” *Id.* at § 2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991); *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986), *cert denied*, 480 U.S. 947 (1987); and *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984).

In this case, the PTO devoted exclusive commentary to the alleged absence of working examples and other illustrative guidance. However, as the discussion in the preceding section and supporting exhibits make clear, *supra*, the skilled artisan would have already known how to select and use precursors of protoporphyrin IX because these precursors were known in the art at the time of invention. Thus, the PTO erred in stating that “the skilled artisan in art [*sic*] would first have to search the prior art and test every compound, known and unknown, for its effect on the production of protoporphyrin IX.” Office Action at page 5. Because the skilled artisan would have known already what compounds would be available as such precursors, he would not have had to search “all of the prior art” and cast about for unknown compounds. Thus, while *some* experimentation might have been incumbent upon the artisan, and therefore consistent with the standard under section 112, it certainly would not have been *undue* experimentation, as the universe of possible precursors was much smaller than what the PTO envisioned in its expansive assumptions. Consequently, the claims are enabled, and Applicants therefore courteously request the PTO to reconsider and withdraw this ground for rejection.

D. Rejection of Claims Under 35 U.S.C. § 112, Second Paragraph

The PTO rejected claims 1, 3, 5, 6, and 11-21 for being allegedly indefinite on the grounds that the phrase “precursor of protoporphyrin IX” does not sufficiently define compounds so as to inform the skilled artisan of the metes and bounds of the claims. Office Action at page 5. Applicants respectfully traverse.

The foregoing discussion and appended exhibits moot this rejection because they evidence that the skilled artisan would in fact know the structures of various precursors of protoporphyrin IX. The artisan would harbor no uncertainty as to what the offending phrase entails, and therefore the claims are not indefinite.

The PTO also rejected claim 5 as being unclear for allegedly failing to specify what is being administered in the claimed method. The amendment to claim 5 moots this ground for rejection.

Finally, the PTO rejected claim 6 for depending from itself. Applicants amended claim 6 to remove the inadvertent dependency, and thereby obviated this ground for rejection.

Accordingly, Applicants courteously urge the PTO to reconsider and withdraw these grounds for rejection.

IV. Conclusion

Applicants believe that the present application as amended is now in condition for allowance. Examiner Badio is invited to contact the undersigned by telephone she feels that a telephone interview would advance the prosecution of the present application.

Respectfully submitted,

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The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.